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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PANDE, SUCHIRA	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,502	KRAMER ET AL.	
	Examiner	Art Unit	
	Suchira Pande	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *02 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/2/04;8/16/04 &10/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II invention claims 9-16 in the reply filed on September 1, 2006 is acknowledged.

This application contains claims 1-7 drawn to an invention nonelected without traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

2. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Fig. 3 lists sequences that are not identified by their SEQ ID Nos. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

3. The disclosure is objected to because of the following informalities: The sequences shown in Fig.3 are not identified by their SEQ ID Nos. Once the Figure is corrected appropriate correction should be made to Brief Description of Drawings section of the specification.

Claim Objections

4. Claim 9 is objected to because of the following informalities: Applicant has elected Group II invention for prosecution. Claim 9 recites analyte utilizing a mixture of claim 4. Further claim 4 depends on claim 1. Both claims 1 and 4 are part of non-

elected group, applicant must rewrite claim 9 to incorporate all the limitations of claim 4 in claim 9. Appropriate correction is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchez, Jr. et. al. (US Pat. 6,500,622 issued Dec 31, 2002) in view of Bonnet et. al. (1999) Proc. Natl. Acad. Sci. vol. 96: pp. 6171-6176 (cited by applicant in the IDS).

Regarding claim 9, Bruchez, Jr. et. al. teach:

*A hybridization assay (*see col. 30, lines 38- 41; col. 38, Example 2 and col. 39 lines 38-44, where hybridization assay is taught) *for a multiplicity of nucleic acid sequences in an analyte* (see col. 31, lines 31-33 where strategies are taught that will allow multiplexing.

See col. 7, lines 42-45 where hybridization to corresponding different target polynucleotide is taught. Specifically see col. 39 lines 58-62 where hybridization assay to monitor much larger number of DNA samples using encoded bead conjugates is taught) *utilizing a mixture of claim 4 (*the limitations of claim 4 which depends on claim 1 will be addressed after limitations of base claim 9 have been addressed*) including steps of:*

a) contacting said mixture and said analyte (see col. 35, lines 6-9, where contacting target sequences with the capture probe and hybridization of target sequence with complementary capture probe sequence is taught. Also see col. 35, lines 20-47 where multiplexed embodiment is taught),

b) forming a distributed array of said microcarriers (see col. 35, lines 55-67 where various methods of preparing microarrays are taught. By teaching method of preparing microarray slides see col. 35 lines 55-56, Bruchez, Jr. et. al. teach forming a distributed array, which is described by applicant as setting the microcarriers, preferably microbeads, onto a planar surface, for example a microscope slide as a distributed array.

c) determining which microcarriers have capture probes hybridized to nucleic acid sequences of said analyte (see col. 31, lines 25-30, where Bruchez, Jr. et. al. teach fluoresecnce is observed as quencher in the capture probe moves away from the reporter fluorescent moiety as a result of binding of the analyte to the capture probe. To begin with all the microcarriers are non-fluorescent. Only those microcarriers that have target analyte bound to them become fluorescent.) *and*

d) optically decoding said microcarriers to identify the sequences of their capture probes (see col. 31, lines 30-51 where conjugation to different colors or color combinations for multiplexing are taught). Bruchez, Jr. et. al. teach signature of the encoded microspheres (referred to by applicant as microcarriers) is detected to identify the nature of the molecular beacon (term used for the capture probes used in the art to describe the probes used in the current invention). Thus Bruchez, Jr. et. al. teach decoding of microcarriers to identify the sequences of their capture probes. This decoding is optical is inherent to the detection system and col. 31, lines 41-51 provide explicit support to this conclusion where *Bruchez, Jr. et. al.* teach use of different region of emission spectrum in the spectral region of interest to encode different microspheres. Also see col. 36, lines 11-15 where laser scanning of arrays using appropriate excitation and emission filters is taught (parameters useful in optical measurements).

Regarding claim 10, Bruchez, Jr. et. al. teaches use of flow cytometer to read results of molecular beacon on a bead assay (see col. 39, lines 39-62. In the assay performed step a) contacting said mixture and said analyte precedes detection step.) In the same assay referenced above Bruchez, Jr. et. al. teaches the encoded beads could be analyzed using a flow cytometer par.39, lines 56-57). It is well known in the art that flow cytometer can be used to form distributed array of beads in flow cells and it is a device that can be used to detect the signals on each beads. In the assay described the binding of analyte to the beads was done in tubes (batch treatment of beads in a reaction slurry) and 20-30,000 of these treated beads were analyzed. Here no preformed distributed array was used. Therefore the experimental design taught by

Bruchez, Jr. et. al. inherently requires that step a) precede step b) of forming distributed arrays. See also col. 40 lines 53-58 where beads were batch treated before being read by flow cytometer. Thus Bruchez, Jr. et. al. teaches the assay according to claim 9 wherein step a) precedes step b).

Regarding claim 11, Bruchez, Jr. et. al. teach the step of decoding includes disrupting said affinity pair by increasing temperature (see col. 35. lines 46-48).

Regarding claim 12, Bruchez, Jr. et. al. teach the step of decoding includes disrupting said affinity pair by addition of a denaturant (see col. 35, lines 9-19 where Bruchez, Jr. et. al. teach use of varying salt concentration to optimize disruption of affinity pairs to allow binding of templates differing in single nucleotide polymorphism). Salt is used as a denaturant in this case. Thus Bruchez, Jr. et. al. teach the step of decoding includes disrupting said affinity pair by addition of a denaturant.

Regarding claim 13, Bruchez, Jr. et. al. teach wherein said distributed array is a planar array (see col. 35, lines 56 where microarray slides are taught. Thus by teaching microarray slides Bruchez, Jr. et. al. teach planar array).

Regarding claim 1, Bruchez, Jr. et. al. teach *a coded microcarrier (*as applied to claim 9 above*) having immobilized on its surface a plurality* (see col. 7, lines 40-52 where plurality of probes conjugated to same substrate is taught) *of quenched, labeled signaling hairpin molecules each comprising an interacting affinity pair separated by a linking moiety, one member of the affinity pair having bound thereto at least one fluorophore and the other member of the affinity pair having bound thereto at least one quencher* (See Fig. 2 where quenched, labeled signaling hairpin molecule each

comprising an interacting affinity pair separated by a linking moiety, one member of the affinity pair having bound thereto at least one fluorophore and the other member of the affinity pair having bound thereto at least one quencher is depicted. Also see col. 3, lines 19-45; col. 21, lines 15-29 and col. 30, lines 26-67 where molecular beacon on a bead is described), *wherein interaction of the affinity pair of each hairpin molecule is disruptable by a physical or chemical change in a condition of its environment (*see Fig. 2 right panel where binding of target molecule to hairpin probe disrupts the interaction of the affinity pair of the hairpin molecule resulting in fluorescence signal to be detected. See col. 21 lines 23-29 where hybridization of target to probe leading to fluorescence emission is taught. Also see col. 31, lines 25-30*)*

*wherein the disruption of the interaction of at least one affinity pair occurs at a first level of said condition and the disruption of the interaction of at least another affinity pair occurs at a second level of said condition (*see col. 35 lines 9-30 where Bruchez, Jr. et. al. teach binding of two SNP alleles to two capture probes. Here different salt and temperature conditions allow for binding of the two targets to their respective probes, thus Bruchez, Jr. et. al. teach the disruption of the interaction of at least one affinity pair occurs at a first level of said condition and the disruption of the interaction of at least another affinity pair occurs at a second level of said condition) , *and where said disruptions are optically differentiable (*This aspect enumerated above for claim 9 in detail also see col. 31, lines 31-40*)*. Thus Bruchez, Jr. et. al. teaches all elements of claim 1.

Regarding claim 4, Bruchez, Jr. et. al. teach:

A mixture of a plurality of coded microcarriers (see col. 30, lines 62-64 where attachment of molecular beacons to encoded microcarriers is taught. Also see col. 31, lines 1-3) according to claim 1 (the limitations of claim 1 have been addressed above) *suitable for use in a distributed microarray, wherein the individual microcarriers each have immobilized thereon a capture probe* (see col. 39, lines 39-42, where coded microspheres (microcarriers) conjugated to four different molecular beacons is taught. Also see fig. 2) and

wherein the coding scheme (see col. 18, lines 4-67 and col.19, lines 1-30 where Bruchez, Jr. et. al. teach spectral coding system*) for identifying individual microcarriers in said mixture comprises a combination of from three to eight spectrally deconvariable fluorophores* (see col. 24, lines 48-59 where Bruchez, Jr. et. al. teach a long list of fluorophores covering the whole visible spectral range from violet to red colors. This list includes more than three to eight fluorophores which have the emission maximum in that are known in the art to be spectrally deconvariable (as evidenced by Tyagi et. al. (1998) Nat. Biotechnol 16:49-53 Table 1 and page 51 par. 2) (cited by applicant in the IDS)). Bruchez, Jr. et. al. teach use of DABCYL as a quencher that can be paired with the fluorophores to form the combinations recited above (see col. 30, lines 48-56) *and at least three affinity pairs disruptable at detectably different levels of said condition* (see col. 35, lines 9-14 where Bruchez, Jr. et. al. teach how a single nucleotide polymorphism is sufficient to prevent mismatched probe from being accessible for hybridization. In col. 35, lines 15-19 Bruchez, Jr. et. al. goes on to teach factors important for optimizing the assay to detect single nucleotide polymorphism, which

include factors such as assay temperature and assay salt concentration. In col. 35, lines 20-48 Bruchez, Jr. et. al. teaches two affinity pairs that allow detection of two alleles of the SNP depending on temperature.

Regarding claim 4, Bruchez, Jr. et. al. does not teach *at least three affinity pairs disruptable at detectably different levels of said condition.*

Regarding claim 4, Bonnet et. al. teaches at least three affinity pairs disruptable at different temperature as shown in Table 1, page 6175 where probe target duplexes containing three mismatches A-A; C-A; and G-A is taught. The mismatch leads to change in melting temperature for dissociation of probe from target duplex. Perfect match TA has a melting temp of 42°C. While G-A mismatch dissociates at 28°C; A-A mismatch dissociates at 27°C and C-A mismatch dissociates at 23°C. Thus Bonnet et. al. teaches at least three affinity pairs disruptable at detectably different levels of said condition. Thus Bruchez, Jr. et, teaches all elements of claim 4. al. and Bonnet et. al.

It would be *prima facie* obvious to one of ordinary skill in the art at the time of this invention to combine the affinity pairs taught by Bonnet et. al. with the affinity pairs taught by Bruchez, Jr. et. al. The motivation to do so is provided by Bonnet et. al. who demonstrated the advantages of molecular beacons namely ability to readily distinguish targets that differ by only a single nucleotide over the conventional probes (see page 6171 par. 3). Using thermodynamic approach they explained why molecular beacons provide higher sensitivity to the presence of a mismatch at the same time they are insensitive to variations in identity and position. These features greatly simplify the detection of point mutations (see page 6176 par. 1). Finally they state " Molecular

beacons can be used for simple and accurate genetic analyses in which single-nucleotide polymorphism need to be detected" (see page 6176 last par.).

8. Claims 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchez, Jr. et. al. (US Pat. 6,500,622 issued Dec 31, 2002) and Bonnet et. al. (1999) Proc. Natl. Acad. Sci. vol. 96: pp. 6171-6176 as applied to claim 9 above in view of Fan et. al. (US Pat. 6,890,741 filed on July 24, 2001).

Regarding claim 13, Bruchez, Jr. et. al. teach assay of claim 9 and teach micro array slide but do explicitly use word planar array to describe the distributed array.

Regarding claim 13, Fan et. al. teach planar array.(see col. 16, lines 21-22 and col. 33, line 22).

Regarding claim 14, Fan et. al. teach wherein planar array comprises microcarriers affixed to the ends of fibers of a fiber-optic bundle fiber–optic bundles (see col. 3, lines 34-47 and col. 35, lines 9-11).

Regarding claim 15, Fan et. al. teach wherein distributed array is a linear array. (see col. 32, lines 11-22 where ordered arrays and random arrays are taught. Linear array in a capillary also referred to as spatially directed arrays because beads occupy a spatial position in the linear order in the capillary (see col. 31, lines 60) can be either ordered or random. Thus by teaching ordered arrays and random arrays either of which could be used to form linear arrays, Fan et. al. teach linear array.

Regarding claim 16, Fan et. al. teach wherein steps c) and d) include flow cytometry (see col. 31, lines 59 where flow cytometry is taught as a detection scheme.

It would have been *prima facie* obvious to one of ordinary skill in the art to practice the various arrays taught by Fan et al. in the assay of Bruchez, Jr. et. al. at the time of the invention. The motivation to do so is provided by Fan et. al. who teach a bead based method for multiplex detection of target analyte that is capable of performing millions of assays simultaneously. They state "present invention permits highly multiplexed nucleic acid detection reactions under uniform sample preparation and reaction conditions. That is preferably the method includes multiplexing from hundreds to thousands of assays simultaneously, more preferably up to millions of assays" (see col. 4, lines 18-24).

Conclusion

Thus all claims under consideration 9-16 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
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9/27/07